

While Claims 1, 31 and 33 of U.S. Patent No. 6,057,367 may dominate claims 8-14 of the instant application and therefore provide a *prima facie* case of obviousness, any *prima facie* case of obviousness is rebutted in respect to U.S. Patent No. 6,057,367 on the basis of the following positions.

Consider firstly that Claims 8-14 herein require an inhibitor of glutathione-dependent formaldehyde dehydrogenase whereas Claims 1, 31 and 33 of U.S. Patent No. 6,057,367 require a manipulator of nitrosative stress, and it is not obviousness from U.S. Patent No. 6,057,367 that glutathione-dependent formaldehyde dehydrogenase enzyme even exists and that an inhibitor of glutathione-dependent formaldehyde dehydrogenase is a manipulator of nitrosative stress. In this regard, consider page 2, line 19-page 3, line 5 of the instant patent application which recites:

It has been concluded in the course of making the invention herein that enzyme, namely glutathione-dependent formaldehyde dehydrogenase known heretofore to oxidize the formaldehyde glutathione adduct, S-hydroxymethylglutathione, previously thought to be the major enzyme substrate, functions *in vivo* to metabolize S-nitrosoglutathione and protein S-nitrosothiols to modulate NO bioactivity, by controlling the intracellular levels of low mass NO donor compounds and preventing protein nitrosylation from reaching toxic levels.

Based on this, it follows that inhibition of the enzyme potentiates bioactivity in all diseases in which NO donor therapy is indicated, inhibits the proliferation of pathologically proliferating cells, and increases NO bioactivity in diseases where this is beneficial.

It follows that Claims 1, 31 and 33 of U.S. Patent No. 6,057,367 cannot make Claims 8-14 of the instant application obvious because it does not even teach the existence of a glutathione-dependent formaldehyde enzyme or give any data allowing forming the quoted conclusion, and therefore does not disclose or make obvious the function of glutathione-dependent formaldehyde dehydrogenase relied on for the instant invention, of "metabolizing S-nitrosoglutathione and protein S-nitrosothiols to provide NO bioactivity."

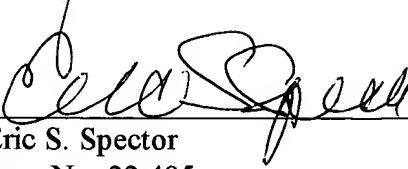
Consider secondly that there is no overlap or structural relation between the specific compounds named for administration in U.S. Patent No. 6,057,367 and the specific compounds named for administration in the instant patent application.

In other words, the Claims 8-14 of the instant patent application are unobvious over Claims 1, 31 and 33 of U.S. Patent No. 6,057,367 because U.S. Patent No. 6,057,367 does not motivate administration of inhibitor of glutathione-dependent formaldehyde dehydrogenase to manipulate nitrosative stress (a) because the function of the glutathione-dependent formaldehyde dehydrogenase that is relevant to Claims 8-14 is not disclosed in U.S. Patent No. 6,057,367 or made obvious thereby and was not known prior to making the invention here (but rather the formaldehyde glutathione adduct, S-hydroxymethylglutathione, was considered to be the major enzyme substrate), and (b) because no structural relation is obvious from U.S. Patent No. 6,057,367 or has been shown, between any compounds administered within the scope of Claim 1 of the instant application and any specific compounds named in U.S. Patent No. 6,057,367.

Allowance is requested.

Respectfully submitted,

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Case Duke File No. 1838

Date: February 28, 2003